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Fundamental Review

"Chemometrics"

by

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in

Analytical Chemistry

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

During the last two years since Chemometrics became a formal entry in the Fundamental Reviews issue of ANALYTICAL CHEMISTRY the topic has been defined, taught, expanded, matured and hopefully, brought at least a few chemists and statisticians and applied mathematicians a bit closer together. As per the international Chemometrics Society, chemometrics is defined as "the chemical discipline that uses mathematical and statistical methods, a) to design or select optimal measurement procedures and experiments; and b) to provide maximum chemical information by analyzing chemical data. In the field of Analytical

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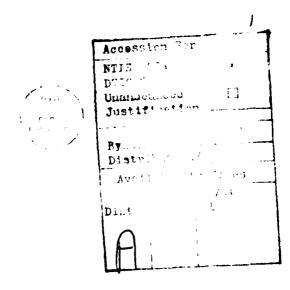S/N 0102-014-6601

Chemistry, Chemometrics is the chemical discipline that uses mathematical and statistical methods for the obtention in the optimal way of relevant information on material systems".

Even in spite of the formidable barrier of having to learn such topics as multivariate statistics, linear algebra and numerical analysis, analytical chemists are becoming increasingly more interested in and aware of the potential rewards application of the tools from this new subdiscipline can provide. Even a casual persusal through this review should serve to convince the reader that analytical chemistry is beginning to mature as an information science and that analytical chemometrics will change the way analytical methods are developed and then applied. (E1), (E5)

The authors prefer to view chemometerics as an interface between chemistry and mathematics. The tools are vehicles that can aid chemists to move more efficiently on the path from measurements to information to knowledge. We hope that this review will serve as a useful punctuation in time by critically examining the development of analytical chemometrics from December 1979, the end of the period covered by the last review (E4), to Decemeber 1981 the end of the period covered by this review. In keeping with the focus of the last review, we will not attempt to review the growing body of chemometrics literature in all fields of chemistry. Rather, the focus will be strictly on analytical chemometrics.

19. Key words:

Image Analysis
Control and Optimization
Pattern Recognition

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EDUCATION

There can be no doubt that a critical shortage of analytical chemists now exists in the world. The prospects of meeting the demand in the near future is not encouraging. In comparison, the shortage of analytical chemometricians trained in analytical chemistry, mathematics and computer science is so critical as to present a hopeless situation. For this reason, and as a sign that chemometrics is achieving more recognition, attention has been recently focused on formally training analytical chemists in chemometrics. At the Fall 1981 American Chemical Society Meeting in New York City a Symposium titled "Interpreting Complex Chemical Data-Teaching Chemometrics" was sponsored jointly by the Divisions of Analytical Chemistry, Chemical Education, and Computers in Chemistry. Two things were apparent at the meeting. First, many chemical educators in colleges and universities are aware of a need to formally introduce chemometrics into their curriculum. Second, the relatively few centers of

formal education in chemometrics that are currently in operation teach only a

selection from the full range of topics in chemometrics. Furthermore, coverage

is weighted towards the current research activities in specific chemistry

departments. It is clear that chemometrics is still in an early state of

development. It would be premature to try to decide which topics within the

field deserve more attention than others at this time. As development continues

and the field matures, topics within chemometrics that have truly provided

significant gains will receive the emphasis they deserve.

In support of the arguements above, it should be noted that chemometrics in

general, and analytical chemometrics in particular, is still without a

textbook. There have been a number of good books on various topics within

chemometrics that chemists will find useful. Kateman and Pijpers book entitled

"Quality Control in Analytical Chemistry" (B1) has received a favorable review.

(B2). The book does not cover what in the U.S.A. is known as quality control.

Rather, it provides an in depth look at the quality of analytical measurements

from the sample collecting stage to data processing. The final chapter even

discusses the organizational aspects of analytical laboratories.

Of a more specialized nature, books written by chemists on information

theory (B3), pattern recognition (B4) and factor analysis (B5) have been

published during the review period. These books should be quite helpful when

chemists decide to learn more about how these topics impact on chemistry.

A number of authors have chosen to express their views on education in

chemometrics in the open literature. Delaney and Warren (E2) have written a thoughtful and enthusiastic article on education in chemometrics in general and their own course in particular. Their experience would be invaluable to anyone wishing to expand a chemistry curriculum. From author point of view, Massart (E6) and den Boef (E3) discuss the potential and importance of a knowledge of computers and mathematics in analytical chemistry. Rogers (E7) states that "analysts should learn enough statistics to enable them to ask statisticans the right questions and to understand the answers they receive". The authors of this review would like to second the motion.

Finally, quite a lot has been written about the use of computers of all shapes and sizes in chemical education. For example, Smith (E8) tells us how microprocessors can be used for simple, low cost, low (psychological) pressure dry lab type experiments. Just as chemometricians find the computer to be an indispensible tool for research, development and application, the computer may become the educational tool in chemometrics as well.

INVASION OF THE MICROS

In the last review in these pages virtually no credit was given to the chemists responsible for providing chemometricians with easy access to their most important tool; the laboratory computer. The mathematics we use has been around for some time but it was not until chemists began interfacing the minicomputer to analytical instrumentation that chemometrics really began to flourish.

There are numerous books and papers written on the subjects of computer interfacing and laboratory data acquisition and analysis. Since a complete review of all of this work over a two year period would amount to doubling or more the size of this review, a selection of recent papers is offered here in order to show the breadth of work in this area and to alert chemometricians to fruitful areas of investigation.

The authors of this review wish to begin with a warning, or at least a strong word of caution. Computers of one size or another can be found on almost all new commercially available analytical instrumentation. In the near future it will be hard to find an unautomated instrument. Computers can calibrate instruments, tirelessly feed samples for analysis, and report concentrations in flashing multi-colored lights. These instruments are both tempting and intoxicating as they will do most of our work for us as obedient robots. The danger is in the total acceptance of the results from automated instruments as

truth. Accuracy is the first goal of analytical chemistry. It is true that automated instruments can usually yield better precision than manual analysis and good accuracy must accompany high precision. However, as every analyst knows, high precision plus a determinist error or an improper calibration method equals garbage. There is no stopping automation in analytical chemistry. However, automation provides a challange of tidal wave proportion to analytical chemometricans in the future. Automation combined with the proper chemometrics will yield accurate chemical information. Indeed, research in error detecting and self correcting intelligent analytical instrumentation currently underway in the authors' laboratory and elsewhere should yield accurate information and cost effective analytical systems.

Stockwell and Telford (IM71, IM2) call automatic data processing in chemistry "a mixed blessing". They call for proper data processing to be an intregal part of automated method development. They also state that the prime objective of automation is an improvement in overall performance which can only come about when the specification of the true analytical needs preceed automation.

Just as analytical instruments are being coupled (IM39) to yield improved measurement systems, computers of all sizes are also being coupled (IM67) to provide improved computational systems. Microprocessors built on the integrated circuit CMOS technology are gradually replacing the more expensive minicomputer for performing instrument control and data acquisition functions. Minicomputers

are becoming more and more powerful and are beginning to replace the large mainframe computers as host computers in computer networks of micros and minis. The analytical chemist is gradually losing interest in the large mainframe computers for at least two reasons. First, the computation power of the laboratory minis is growing and is usually adequate for most data processing tasks. Second, data acquisition rates are becoming so demanding that remote processing requires abnormally high data transmission rates.

Even pocket calculators are now powerful enough for complex calculations (IM52, IM46, IM28). In the future, computer problems will be down loaded to programmable calculators which will control and process data from field instruments.

The analytical chemist wishing to learn more about how the microcomputer revolution will effect analytical chemistry is indeed fortunate as several excellent papers have been written recently by respected analytical chemists (IM70, IM49, IM41, IM9, IM8, IM19, IM23). There is a whole issue of Talenta, 28,7B, 1981, devoted to microprocessors in analytical chemistry. Additionally, general papers on microprocessor based laboratory data acquisitions systems are also available (IM79, IM17, IM57) as well as papers describing more specialized microprocessor controlled hardware (IM10, IM7, IM63, IM24, IM4).

Finally, the important interface between the chemist and laboratory computer systems is receiv attention (IM81, IM56). Dialogue programs and simple command languages will be required if chemists are to take full advantage of the

age of computer automation.

The remainder of this section is aimed at giving the reader a view of the continuing efforts in laboratory automation with an emphasis on microprocessors. This is not a complete view of all of the work in this area.

All areas of analytical chemistry have become targets for computer automation. Although the lion's share of emphasis is with instrumental methods of analysis, even classical methods of chemical analysis can be made more precise, faster and less costly via on-line data acquisition and analysis (IM16). Automation also allows them to be more competitive with instrumental methods.

Electrochemists were probably the first to use laboratory computers. Microprocessors are now assuming such tasks as programmable function generators (IM13) and are used in several different approaches to data acquisition and analysis in polarography (IM2, IM73, IM31, IM30), voltammetry (IM6, IM35, IM76) and coulostatic stripping analysis (IM64). Microprocessor based systems are quite versatile and have the ability to compare more than one type of electrochemical method for a single analysis (IM66, IM1, IM12).

The interest in the electrochemistry of surface processes in monolayers has also been made possible by mini computer automation (IM54).

A most interesting application of microprocessor controlled electrochemistry is represented by the work of Adams and coworkers (IM21,IM35). These workers have been monitoring th' neurotransmitter release in situ in the brains of small

animals by chronoamperometry. Microsensors and microprocessors hold much promise for analytical chemistry in laboratory medicine.

Chromatography is an area that has been automated to the point where samples can be run day and night with a minimum amount of attention. Recent improvements in on-line data acquisition (IM59, IM78), general purpose data processing (IM38, IM43) and specific areas of data processing studies such as hydrocarbon type analysis (IM74) and fatty acid analysis (IM45) continue to appear in the literature.

When chromatographic instruments are coupled to other analytical instruments the computer becomes an indespensible tool just for data acquisition let alone data analysis. GC-MS (IM26), GC-FTIR-MS (IM77), LC-FTIR (IM44) and LC--Flourescence (IM37) are a few examples of this continuing trend. The analysis of data generated by these instrument combinations is reviewed in other parts of this review (e.g., Factor Analysis, Resolution).

Molecular and atomic spectroscopy continue to be impacted by computer rautomation providing important problem areas for chemometricians. Mass spectrometry (IM3), NMR (IM65, IM48, IM27), ESR (IM11), IR (IM60, IM29, IM32), IR/RAMAN (IM47), and flourescence spectroscopy (IM61) have all benefitted immensely from continued investigation in computer interfacing and data analysis.

Microprocessors, alone (IM51, IM69) or interfaced to diode-array detectors (IM50), have lead to vastly improved systems for acquiring chemiluminescence

spectra. In areas of atomic analysis, spark source (IM5) and ICP source (IM53, IM20) atomic emission spectrometry, atomic absorption spectrometry (IM72), neutron activation analysis (IM48) and spark source mass spectrometry (IM58, IM75, IM25) have also benefitted from recent studies involving computer automation.

Kinetic methods of analysis are obvious benefactors of the laboratory computer. The faster spectral data can be acquired, the faster the reactions to be used for analysis can be. Several recent publications demonstrate the benefits that can accrue (IM68, IM62, IM40, IM14, IM55, IM34, IM80).

Among the new and rapidly growing methods of surface analysis, computer-ization recently has affected secondary ion mass spectrometry (IM22), depth profiling Auger spectrometry (IM36) and photoelectron spectrometry (IM18). Since data can be obtained in two or three (depth) spatial dimensions as well as one or more spectral dimensions progress in surface analysis instrumentation will provide the most difficult challenge to chemometrics in the future. The reader is directed to the section on image processing for more on this topic.

Finally, although it is currently recognized by only a handful of analytical chemists, computer automation has opened up a career direction that is perhaps the most demanding yet potentially the most rewarding of anything yet seen by the analytical chemist; closed loop, optimized, industrial process control (IM42, IM33, IM78). Chemical engineers have become quite adept at completely automating industrial processes. One would like to think that an automated

system is an optimized system but this is not generally true. In order to optimize a process, the computer needs to have accurate, current estimates of a so called target variable (e.g. product yield). This calls for on-line chemical analysis with sufficient sensitivity and accuracy to detect changes in the controlled target variable as a function of the controllable variables (i.e., feed flow rates, temperature, etc.). When more analytical chemists are willing to leave the security of their laboratories and learn chemometrics and control theory, their futures will be enhanced accordingly.

STATISTICS

During the past two years, the literature of analytical chemistry has
witnessed quite a number of good papers dealing with topics of fundamental
importance to our field; measurement errors, accuracy, precision and measurement
characterization in general. All analytical measurements are really random
variables and therefore the information (e.g. analyte concentrations) we gleen
from these measurements is uncertain. In spite of this fact, the vast majority
of analyses are done with little thought of expressing the uncertainity in the
estimates of analyte concentrations with the aid of the tools of statistical
analysis.

A former author of this review, under a different title, has recently drawn
attention to the connection between the uncertainty of analytical data and
societal decisions (S6). This paper should be required reading for all students
of analytical chemistry.

The uncertainty in analytical measurements is usually referred to as error
or noise and can come from many sources. Round-off error (S30) from quantizing
measured values to few significant figures can distort the information conveyed
by the measurements. Belchamber and Horlick (S2) have shown that digitization of
analog signals can introduce distortion via quantization effects. In fact, when
noise is less than about one-half of the quantization level, random noise must
be added to analytical signals before signal averaging. Systematic errors can

result from such sources such as improper selection of volumetric glassware (S22) and the use of analog integration in the widely used controlled - potential coulommetry (S17).

A number of useful reviews of standard statistical methodology as well as proposed measures of reliability have been offered (S3, S20, S26). Major problems can result when these standard procedures are used and the frequency distributions assumed to represent the analytical error are not correct (S34, S29).

A direct approach to estimating the uncertainty in chemical information as a function of measurement error is a straight forwara propagation of error calculation of one form or another. This approach is highly recommended and has been sucessfully applied to the important topic of speciation (S32) as well as electrochemistry (S14), chromatography (S12, S31) and spectrophotometry (S19, S9, S27). Accuracy and precision in analytical chemistry are subjects of perpetual concern in analytical chemistry. Recently they have been addressed in a general manner (S36, S7, S18) and also with regard to specific analytical techniques such as the cell shift method in molecular fluorescence (S5).

Algeo and Denton (S1) have published the results of an impressive study in the error propagation involved with using the inverted Abel integral equation to evaluate spectroscopic sources. They found that the selection of one of three methods tested depends upon the noise level and number of data points available.

Signal to noise measurement characterization is another important topic in

analytical chemistry. Interest in this topic has always followed the development of a new analytical method as evidenced by a recent investigation of this nature in Fourier transform mass spectrometry (S35). Signal characterization can also amount to a rather complex and detailed study such as the one reported by Smit and coworkers (S8). They used autocovariance and power spectral density to study noise from the nebulizer and the emission signal in ICP - atomic emission spectrometry. The reader is referred to that reference and the section of this review dealing with Spectral Analysis for more details on this approach.

Other tools of statistics have also received attention of greater or lesser degree from analytical chemists. An excellent and highly recommended discussion on sampling theory has appeared on the "A" pages of ANALYTICAL CHEMISTRY (S21). It is rather surprising that more does not appear on this topic.

The logical and optimal design of experiments using factorial designs has fortunately seen increased activity since the last review. Factorial designs have been used with success in chromatography (S33), the enzymatic determination of arsenic V (S23) and for the analysis of kinetic data (S13). It is indeed unfortunate that the development and optimization of a new analytical method does not always include a good experimental design. The reader is referred to the section of this review dealing with analytical method optimization as experimental design and response surface and optimization methodology usually go hand-in-hand.

A few good critical papers have recently appeared warning analytical

chemists to view statistical parameters with caution (S24, S25). Moore (S24) correctly states that correlation should not be used to deduce a causal relationship. Rothstein and coworkers (S28) conclude that the jacknife test is superior to Kendall's and Spearman's s statistic for the problem of NMR structure determination using lanthanide shift reagents.

Finally, information theory (S10, S11) and time series analysis (S31) continue to see application in analytical chemistry and statistical decision theory (S15, S16) has been newly proposed for application.

MODELLING AND PARAMETER ESTIMATION

This section and the Calibration and Resolution sections that follow are
closely tied together. In the most general sense, the aim of the papers
reviewed here is to model a chemical system in a computer. The model can be
empirical or derived from theory and consists of one or more mathematical
functions fit to a collection of experimental data using some method of
parameter estimation. The parameter estimation methods most frequently used
are linear and nonlinear least squares.

Once the model is selected and the estimated parameters of the model are
found to give a useful and accurate estimation of the experimental data, the
model can be used to help understand the dynamics system or predict its
behavior under different conditions. As will be seen in this section, several
chemical systems can be accurately modelled. Also, there are many different
models and model transformation and parameter estimation methods from which to
choose.

Calibration is perhaps the most straightforward and oldest kind of
modelling used in analytical chemistry. Historically, the response of an
analytical sensor is related to concentration via a linear relationship. Para-
meter estimation involves finding the slope and interecept of the line with a
ruler or a computer. In view of the importance and recent activity in research
on calibration, this type of modelling is reviewed in a separate section.

Resolution may also involve modelling, parameter estimation and verification. For example two compounds elluting from the column of a gas chromatograph will appear as two overlapping bell shaped curves. The individual curves can be modelled by modified gaussian functions and a sum of two functions fit to the overlapping peak data. If successful, the parameter estimation will resolve the exact locations in time where each compound elluted as well as enough parametric information to allow integration of each component separately. Again, due to the importance and activity in this area over the past two years, resolution is reviewed separately from this section.

The scope and limitations of modelling (often called curve fitting) in spectrocopy is the focus of a paper by Maddams (M26). Although resolution of overlapping bands is a primary focus of the paper, other important topics such as baseline effects and goodness of fit estimates are also discussed. In another paper, Schwartz (M32) reminds us that when more than one parameter is estimated by a parameter estimation method the uncertainty of the parameters is linked via the correlation between parameters. This is a useful paper and contains quite a lot of information that should be understood by anyone interested in modelling of any kind. At this point the authors would like to suggest that analytical chemists wishing to improve their own research by learning and incorporating more chemometrics should read the earlier reviews on Statistics in the Fundamental Reviews in ANALYTICAL CHEMISTRY. These pages are rich in chemical applications of powerful statistical concepts and tools

which unfortunately seem to be lacking in current research publications.

Among the many modelling applications recently performed by analytical chemists, the study by Vandeginste (M40) is perhaps the most unusual. In this study, a routine structural analysis laboratory is modelled by modern digital simulation methods. Histogram and cross correlations of the sample output from a real laboratory agree with the output from the simulated laboratory in several respects. The effects of the introduction of an adaptable sample routing procedure, several techincian assignment decisions and strategies on the termination of the analysis are simulated. This paper should be read by all laboratory directors.

Modelling thermodynamic equilibiria has been shown to be most effective as is evidenced in past reviews. Multiparametric modelling of this type continues to be of interest for potentiometric titrations (M29, M38, M42, M8, M9).

Kinetic modelling with multi-response data in oil shale pyrolosis is the subject of an excellent paper by Ziegel and Gorman (M43). In other kinetics modelling applications enzyme kinetics via a graphical tehnique (M7) and curve fitting of orthogonal polynomials (M30), the kinetics of ion exchange (M21) and phosphorescence decay kinetics (M25) are representative of the high quality work being done by analytical chemists. In more general papers, the linearization of first-order kinetic analysis (M33) and the noniterative analysis of competing reactions by a constant time interval method (M2) should

provide interesting reading to chemists using kinetic methods of analysis.

A modest amount of nonresolution types of modelling research is seen in electroanalytical chemistry. Legget (M22) has shown how nonlinear least squares can yield stability constants from polargraphic data. Model transformation representing transient potentials in ion selective electrodes (M34) and electrochemical simulation studies (M23, M3) have also been reported.

Modelling of one kind or another has also been of interest in molecular and atomic spectrometry. Papers of general interest include the introduction of a theory of measurement (M16), a comparison of various parameter estimation methods in Mossbauer spectrometry (M35) and the development of two new nonlinear least squares algorithms (M27, M10). In more specific studies modelling and parameter estimation have been combined to calibrate dye lasers with simplex least squares (M1), simulate temperature and pressure effects in photoacoustic spectroscopy (M6), predict changes in spectral peak locations and quantum efficiencies arising from solute-solvent interactions (M17), calculate discharge current waveforms in high voltage spark sources (M31) and improve the precision of intensity measurements in ICP-atomic emission spectrometry (M20) and Fourier transform infrared spectroscopy (M14).

The optimal methods for parameter estimation are of continuing interest to analytical chemists. For example, weighted and unweighted least squares fits have been compared for use in the phase plane method for estimating mean luminescence life times (M12).

A number of good modelling studies with very different goals have been reported in chromatography. In two papers, Smit and coworkers (M36, M37) use modern computer simulation modelling to examine the fundamental aspects of nonlinear non-ideal chromatography. Others have used modelling methods for peak detection (M15) and peak characterization in GC and LC (M24, M11, M4). In other interesting studies, it has been shown that the retention time of an unretained solute can be obtained from C_1-C_5 n-alkane data and the carbon number of the solvent (M28) and that a well known structure-activity method can be used to relate molecular structure to retention index data (M19, M5, M41)

Modelling has also been applied to fundamental studies in ion exhange chromatography. For example, heterogeneous protonation equilibria of chelating exchange resins has been modelled by a linear relationship between the degree of dissociation of the resin and the concentration of the counter ion in the resin phase (M39). Other analytical column processes have also been successfully modelled (M13).

Finally, it should be mentioned that if a model's accuracy can be verified, then the chemist can be quite bold in selecting good candidate studies. For example, Issahary and Pelly (M18) have used the composition of raw materials (MgO, SiO_2, SO_3 and Al_2O_3) to model the grade of a product (P_2O_3) produced by an industrial process.

RESOLUTION

In this section methods for the resolution of overlapping peaks or waveforms

representing pure analytes are reviewed along with applications of these methods

to electrochemistry, spectroscopy and chromatography. As there are numerous

approaches to the age old resolution problem, this section of the review

overlaps strongly with other sections. The reader specifically interested in

resolution should read at least four other sections in addition to this section.

The Calibration section reviews a few methods that actually combine resolution

with the calibration and analysis (e.g. the Generalized Standard Addition

Method). The Spectral Analysis section includes all approaches to spectral

resolution using the Fourier convolution theorem. Also, the Modelling section

deals with the methods at the heart of most resolution approaches. Namely,

peaks or waveforms representing pure analytes are modelled with an appropriate

mathematical function and then a combination of these functions, one for each

analyte, is fit using some parameter estimation algorithm. Finally,

multicomponent resolution based on the powerful method of principal component

factor analysis is reviewed in the section on Factor Analysis. In those

sections, we review papers dealing primarily with the selection of models and

the testing or development of algorithms. Here, we review papers focussing on

resolution as an end goal.

Several of the methods reviewed below are rather general and can be applied

to resolution problems beyond the scope of the papers in which they were first introduced. For example, linear programing (R24) has been applied to the problem of resolving multiple simultaneous exponentials as seen in flourescence decay experiments as well as multiple unresolved Gaussian functions representing peaks of one kind or another.

In spectroscopy, several new approaches to resolving multicomponent mixtures have been developed. Knorr and Harris (R10) have developed an interesting method for resolving multicomponent fluorescence spectra by a two dimensional (emission wavelength and decay time) approach. Their iterative method of data analysis produces unambiguous emission spectra for each individual component even when lifetimes differ by much less than an order of magnitude. The method does not rely on a priori knowledge of the identity of the components.

In another paper, Fogarty and Warner (R7) offer a simple but effective method for resolving multicomponent fluorescence spectra. Their method requires that each fluorescing component have a unique spectral region with a reasonable S/N ratio and that a method be available to alter the relative ratios of the components ⌐ the mixture. The latter can be done by solvent extraction, preferential volitalization or the use of nonselective fluorescence quenchers. Spectra produced by a sample perturbation method are then ratioed to find plateau regions which yield analyte concentration ratios used to generate the spectra of the pure components. A closely aligned method has also been applied to the resolution of powder diffraction data of mixtures (R6).

A method based on using orthogonal functions to model sections of absorption spectra has been in use in the spectrophotometric analysis of pharmaceuticals since the early 1960's. This method is useful when the analytes are known and interfere with one another via spectral overlap. It has recently been applied to differential spectrophotometry (R4), the analysis of thianine hydrochloride (R23) and the simultaneous determination of nifuroxime and furazolidone (R9) in pharmaceutical formulations.

In other areas of molecular spectrometry, new resolution methods have been developed for electron spin resonance (R5), Mossbauer (R15) and infrared spectrometry (R16, R17, R8).

In chromatography the resolution of overlapping peaks caused by closely elluting compounds continues to be a severe problem. Advances have been made in the application of the Fast Fourier Transform for determination of the number of components (R14) and the maximum likelihood method of parameter estimation for mathematically modelled peaks (R20). The detection of variation in peak shape from contamination or overlapping peaks can be done using the distribution function method of Rix (R19). It has also been shown that TLC resolution can be improved using derivative recordings (R22).

When the components to be resolved are known, the detector response for each component at various times can be fit to a second-order polynomial of the components' concentration (R13). A series of nonlinear simultaneous equations are then solved for the concentration of each component in a mixture.

When more spectrometric data can be obtained (e.g. GCMS, LCUV) during a chromatographic separation, vastly improved resolution may be obtained. The simple determination of peak purity by ratioing spectral data accross a peak is an example (R18). Harris and coworkers (R11) have applied their iterative resolution method to the GCMS resolution problem. Trial retention times are used with chromatographic response theory to simulate individual chromatograms. These data are then used to extract the mass spectra of the pure components in a mixture via linear algebra. Once again, the reader should see the Factor Analysis section for more approaches along this line.

For quantitation in electroanalytical chemistry to be successful, overlapping peaks or waveforms must first be resolved. In one approach, Liu (R12) uses six simultaneous equations to resolve overlapping anodic-stripping voltammograms. The use of the Kalman filter (R3) is very effective at determing the number of components within a mixture and has been successfully used to resolve electrochemical peaks (R2).

As stated in the Modelling and Parameter Estimation section, one of the most effective methods for resolving overlapping waveforms is to find accurate models and use a reliable parameter estimation method. Toman and Brown (R21) have published a good example of just such an investigation. They use the hyperbolic secant function and the Simplex optimization method to resolve semiderivative voltammograms with excellent results.

In another approach, Fourier transformed square-wave voltammograms of pure

analytes are fit in the frequency domain to mixture spectra (R1). Two

advantages accure; a less complex fit as the spectra density is condensed to the

low frequencies and the advantage of having the real and imaginary parts to

provide a better average fit.

CALIBRATION

In analytical chemistry, calibration involves a very special type of modelling and parameter estimation; chemical measurements (e.g. voltages) are converted to chemical information (e.g. concentrations of analytes).

There is little doubt that the ideal calibration model is $R = K C$ where R is a measurement of sensor response, C is the analyte concentration and K is the response constant (slope of the calibration curve). For this model to hold true, and for it to be useful, the analytical sensor must not be sensitive to interfering components in the sample and matrix effects must be absent. The former changes the model to $R = K_A C_A + K_I C_I$ where K_A and C_A correspond to the analyte and K_I and C_I the interferent. The $K_I C_I$ term give rise to a non-zero intercept if K_I and C_I do not change during analysis. If they are known the product can be subtracted from R. This is the same operation as in background subtraction.

In the above discussion, R is the response from a single sensor. Ratzlaff (C17) has convincingly demonstrated that there are advantages to be gained when several sensors (e.g. the absorbances at several wavelengths) are used instead of just one.

A matrix effect corresponds to a change in K_A from calibration to analysis. Using the well known standard addition method will eliminate matrix effects as calibration is done in the sample.

Chemists continue to explore improvements to this calibration step in chemical analysis both to eliminate matrix and interference effects and to extend calibration models. Some very fine papers provide comments and cautions on topics such as linear models with zero intercepts (C5), using correlation coefficients to evaluate calibration curves (C19), using single point calibration methods when the intercepts are significantly different from zero (C1) and assuming that measurement variance is independent of concentration (C6).

Topics such as calibration precision and error introduction have been studied in GC/MS (C16), potentiometry (C13) and chromatography (C2). Calibration methods have been reviewed for use in IR spectrometry (C20) and improved for use in TLC (C4) and the determination of the molecular weight of polymers (C14).

By continously extending the working range of a linear calibration curve into a nonlinear range, the usefulness of an analytical method can be increased significantly. Good examples of errors that can accured and methods for extension are found in gas chromatography (C9) and atomic absorption spectrometry (C10) and a general purpose iterative procedure has been developed for the method of standard additions to overcome the linear response constraint (C15).

New methods for dealing with the matrix and interference effects described above are always needed. Recently, methods to handle interferences effects (C18)

and matrix effects (C7, C3) in x-ray flourescence analysis have been reported.

The general method developed to allow accurate analysis in the presence of both matrix effects and interference effects has been improved during the last few years. The method is the multivariate (multianalyte) extension of the standard addition method and is called the Generalized Standard Addition Method (GSAM). Several new variations of the GSAM have been proposed and a theory of multianalyte chemical analysis has had a beginning in a recent report (C11). The method has also been applied to spectrophotometry (C11), ICP-atomic emission spectrometry (C12) and anodic stripping voltammetry (C8).

SPECTRAL ANALYSIS

Many of the instruments used by analytical chemists yield spectra or

waveforms in one form or another. The difference between a spectrum and a

waveform is not terribly important and the two are often interchanged. A

spectrum usually is a result of a dispersion operation as when polychromatic

light is dispersed in a monochromater and light intensity is plotted verses

wavelength. Waveform is a more general term for the plot of a functional

relationsip between two variables (e.g. current verses voltage in stripping

voltammetry). Unlike chemists, engineers make a clear distinction between the

two. Methods of spectral analysis are many and are generally used to either

enhance certain desirable features of spectra or extract specific information

from same. Many of the methods are based on the well known Fourier transform

and, as the spectra are usually processed in digital in a computer, the Fast

Fourier Transform (FFT) was an important development in the mid-1960's.

During the period covered by this review, some generally useful papers have

been published that should be helpful to anyone interested in processing spectra

with a computer. The practical aspects of computation with the Fourier

transform is the subject of a good Instrumentation article in ANALYTICAL

CHEMISTRY (SA18). In another paper, the theoretical signal-to-noise ratio

enhancement from spectral accumulation in Fourier transform NMR is challenged

(SA15). The digitization noise and so-called "mathematical noise" of the

Fourier transform operation must be considered as well as instrumental noise for complete understanding.

The convolution theorem in Fourier analysis is one of the most powerful spectral analysis tools available. It has recently been used to increase mass resolution in Fourier transform mass spectrometry by eliminating phase distortions which were previously minimized by computation of magnitude spectra rather than absorption mode spectra (SA19). The convolution theorem yields the useful process known as deconvolution leading to a powerful tool for spectral resolution enhancement. Fourier deconvolution has been compared to the first-order derivative method for studying intrinsically overlapped band contours (SA14) and has also been succussfully applied to resolution enhancement in polarography (SA10) and spectroscopy (SA13).

Spectral smoothing is another goal of modern spectral analysis. One form of smoothing is Fourier smoothing in which a spectrum is Fourier transformed to the frequency domain, the high frequency coefficients are set to zero (low pass filtering) and the result is inverse Fourier transformed. Elimination of high frequency information usually yields a smoother spectrum. Aspects of the frequency domain cutoffs have been studied (SA16) and this method has been applied to UV Circular Dichroism spectra (SA5). Simple low pass filters have been designed for spectral analysis (SA25) and ultra low frequencies have been filtered in order to remove baseline variation (SA1).

Polynomial smoothing methods (SA28) are also of current interest in spectral

analysis. A good recent paper to read on the most popular polynomial filter, the Savitzy-Golay filter, has been written by Bromba and Ziegler (SA3). The paper contains application hints and its fundamental properties are discussed. Polynomial smoothing using an extended sliding least squares approach has recently been applied to x-ray photoelectron spectra (SA22).

Another well known filter, the Kalman filter has been applied to on-line linear drift compensation (SA21). This method can be applied with success even when the presence of drift in the spectrum is uncertain.

Another goal of spectral analysis is information compression. This is particularily important in spectral search systems as it is desirable to store many thousands of spectra and data compression with minimal information loss can yield savings in storage cost as well as search time. Recent advances in mass spectral (SA17), IR (SA9) and near IR (SA6) data compression have been reported.

The application of on-line digital spectral analysis is changing the way analytical instrumentation acquires spectra as well as the spectral data analytical chemists examine visually. Correlation chromatography (SA23, SA24, SA20) is a good example of the former. Multiple sample injections yield raw chromatograms that are usually too complex for visual analysis. However, cross correlation with the imput injection pattern yields significant improvements over single injection chromatography. Correlation based methods are also showing clear advantages in time resolved fluorimetry (SA12), electron spin resonance spectrometry (SA11), for correlating proton chemical shifts by two-dimensional

FTNMR (SA2) and peak detection in GCMS (SA4).

It is well known that differentiating spectra can lead to sharper peaks. A good paper on second derivative IR spectrometry (SA26) demonstrates the benefits that can be accrued. Improved methods for numerical differentiation of spectra (SA8) promise to make spectral derivatives more common.

Finally, analytical chemists are applying spectral analysis methods in many other diverse studies. The ranges of methodology and application are too broad to be reviewed here exhaustively. DeLevic (SA7) has calculated the sampling error involved in electrochemical Fourier and Hadamard transform measurements. Inherent in these a.c. measurments is a filtering action that takes place because the signals are sampled over a fixed time period. A long sampling period is often tempting as the low frequencies are usually of greater interest. A knowledge of the sampling error is most useful in these experiments.

In another study (SA27) a low resolution version of Fourier transforming IR spectra sampled on-line from GC-FTIR is compared to an orthoganolization approach for detecting effluent spectra in the presence of useless baseline spectra. The methods are tested for execution time and overall accuracy.

IMAGE ANALYSIS

When spectral intensity is measured against one variable such as wavelength
we refer to the graphical representation of the relationship as a spectrum. The
running variable can be wavelength, time, distance or any other variable that
may yield useful chemical information. When spectral intensity is measured as a
function of two running variables (e.g., emission and excitation wavelengths as
in videofluorometry) the resulting 3-dimensional relationship is referred to as
an image. A graphical representation can take the form of a three dimensional
plot or as in a more useful way as a picture where spectral intensity is
represented on linear grey scale; low intensity is shown as a lighter grey than
high intensity.

Many of the same methods applicable to spectral analysis are also applicable
to image processing. Furthermore, images can be acquired and analyzed in higher
dimensions than two. Morrison and coworkers (IA1,IA2) continue to pioneer the
use of image processing methods in analytical chemistry. Their computerized ion
microscope is capable of aquiring and displaying elemental distributions in the
sub-parts-per-million range over the surface of a sample with a spatial
resolution of one micrometer.

Chemical image acquisition and analysis has also been recently initiated in
other areas of analytical chemistry. Two-dimensional gel techniques combined
with digital image processing techniques promise improved resolution of protein

separation (IA4).

Using a digital SIT vidicon to acquire images of fluorescing materials separated on thin-layer plates, rapid, in situ qualitative and quantitative information allows the analyst to take full advantage of the parallel processing capabilities for routine analysis (IA3). A dynamic range of over 500:1 in flourescence intensity can be obtained on a single plate with detection limits in the low picogram range for some compounds.

As analytical chemists become aware of the power of image processing methods used so effectively in such fields as medicine and space exploration the development of chemical image acquisition systems will increase and the number of applications will grow. The development of inexpensive arrays of core memory and array processors will spur development and application.

FACTOR ANALYSIS

The powerful multivariate analysis methods of principal component analysis
from statistics and the slightly broader factor analysis from the social
sciences continue to receive the attention of analytical chemists. As in the
field of pattern recognition, the interest of analytical chemists and the
broad applicability of the techinque has lead to a review book on the
methodology also suggesting various possibilities for chemical applications.
Malinowski's book (B5), though it does not give a complete view of all sides of
factor analysis, will help chemists become familiar with this method.

Two main groups of factor analysis applications can be distinguished in
chemistry. Namely the extraction of underlying, non-measureable factors from
multidimensional data in order to understand the influence of these factors on a
system and the resolution of multicomponent mixtures by spectrum analysis.
Advances in these two areas are reveiwed in this order in the following.

The theory of error in target factor analysis has been used to calculate the
root-mean-square error in factor loadings (F17). The method was tested using
data from gas-liquid chromatography and gave similiar results to the more common
"jacknife" method. The theory of error also was used to show how errors mix into
the target procedure and to develop a criterion to judge the degree of
acceptability of pure targets (F18).

Relative abilities of single and dual substituent parameter scales in

reproduction of substituent effects on magnetic resonance parameters were investigated (F20). Principal component analysis was used to determine the weight (importance) of the measurements.

Historically, the main field of application of factor analysis in analytical chemistry is chromatography. Recently, factor analysis was successfully applied by an iterative method in liquid-solid absorption chromatography, where half of the data were missing (F8). Data analysis applications where several measurements are missing are all to common and methods to handle this problem are in need. Linear free energy relation parameters (e.g., Hammet, Hansch constants) in combination with topological parameters were investigated by factor analysis and multiple regression for their predictive value for GLC retention indices (F3). The influences on the behavior of saturated and runsaturated hydrocarbons in gas-solid chromatography on ion-exchange resins in different cationic forms was studied by correspondence factor analysis (F10). Corr?r?respondence factor analysis is a useful variant of factor analysis.

Source profiles of two phases were determined on the basis of neutron activation analysis of 29 elements of samples from Borax Lake (F21). By weighted least-squares, the rate of convergence was improved in target transformation factor analysis and two factors were extracted.

In another study factor analysis was applied to Delaware Bay sediments using a data set of 18 trace metal concentrations (F2). The three factors extracted were: natural background and oceanic and estuarine sources.

Minerological changes during benficiation of phosphate ore by calcination and washing were studied by applying oblique rotation (F13). Several important mineralogical results were obtained including, for example, the possibility of distinguishing between different contributions to the CO_2 variance.

A matrix of fluorescence lifetime data was investigated as a function of solvents and solutes (F6). Two factors were found sufficient to reproduce the experimental data within experimental error; the identity and number of carbon atoms attached to the exocyclic nitrogen. This paper is a model study as the investigators strive to understand the chemical significance of the calculated factors.

Matrix effects in atomic absorption and inductively coupled emission spectrophotometry have also been studied with the help of factor analysis (F14). The primary goal of the study was the determination of Ta and Ni in gold.

In multicomponent resolution, factor analysis has seen the most application in spectroscopy and chromotagraphy. For exaample, it was used to determine the number of unresolved components under a GC peak. The factors were then used to calculate solution bands for the parent mass-spectra (F22) thereby providing complete qualitative resolution. Along these same lines, factor analysis was applied to identify a second species in a single gas chromatographic peak (F4). Locations of spectra of the constituents on a plot of non-negative values of spectral lines in the factor space can be identified and recognizable spectra of the separated constituents can be given.

The performance of factor analysis for determining the number of components under a chromotagraphic peak was critically evaluated on simulated Gaussian curves (F23). The detection limit of an impurity in the main component peak depends highly on noise of the measurements. Criteria for evaluation of the eigenvalues, imbedded error and indicator functions were given.

Compatible and incompatible blends of polyphenylene oxides and polystyrene can be distiguished by factor analysis of FTIR spectra. A third factor of induced conformation can be detected in the case of a compatible blend, where there are only two factors in incompatible ones (F12).

Factor analysis can also yield information on reaction stoichiometry and the number of reations from FTIR evolved gas analysis (F15). Applications were made in the examination of polymer chain length, intermolecular interactions and in functional group analysis. Target factor analysis error criteria were applied to FTIR spectra to determine, without prior knowledge of the experimental error, the number and identities of components in multicomponent mixtures (F19). The method was compared to regression analysis.

Principal component analysis has been used to analyze Raman spectral data of sulfuric acid/water mixtures in different concentrations to identify different ions, compositions and hydrates (F7).

Data reduction was performed by calculating eigenvectors from spectrophotometric data of multicomponent mixtures (F16) to enable a chemist to use a small desk computer for making nonlinear least-squares fits based on the

Newton-Gauss Marquardt algorithm. Representation of kinetic curves as linear combinations of eigenvectors was described.

The number and identity of species present in binary and tertiary mixtures of polycyclic aromatic hydrocarbons were determined by principal component and decomposition analysis of molecular fluorescence spectra (F9). The authors were very through in examining the problems caused when mixture spectra are highly correlated. Further work has appeared on using matrix rank annihilation (F5) and other multivariate strategies (F1) based on factor analysis to analyze two-dimensional molecular flourescence data generated by a videofluorometer.

Finally, factor analysis is based on the assumption that factors are composed of linear combination of measurements and that factors are independant of one another. While this is a useful approximation it is often true that comp'ex chemical systems are multivariate and nonlinear. Methods for seeking nonlinear factors have recently been introduced to chemistry (F11).

PATTERN RECOGNITION

Following the boom of chemical applications in the 1970's, pattern
recognition continues to be a challenging field of study for chemometricians. A
good introduction to this topic for the uninitiated has appeared recently (P10).
as well as a useful book (B4) on pattern recognition in chemistry. A summary of
the book was presented as a paper at a COBAC conference (P33). A more recent
survey of the application of pattern recognition in analytical chemistry
contains 130 references (P17).

Some new pattern recognition methods have been introduced to analytical
chemists during the past two years. The method of potential functions is shown
as a useful supervised learning techinique, that is density type method
commercialized in the ALLOC software package (P4). Compared with other
classification methods it is shown to perform very well. The applicability of
potential functions as part of a new clustering technique called CLUPOT has also
been investigated on four data sets (P5); the results gave reliable clusters.

A simple vector model was developed (P15) to identify weathered oil samples
based on their fluorescence spectra. This model applies angular distance in
n-dimensional space as a parameter of comparision. The vector of the unknown is
projected on the hyperplane formed by the spectra of unweathered and
laboratory-weathered oils to determine the best fit.

A very interesting pattern recognition method was published by Yeung (P35)

involving audio representation of multivariate chemical data. Each measurement in the data vector was translated into an independent property of sound. A trained ear was able to classify the test set perfectly.

A short introduction to the computational practice in pattern recognition (P18) has been written, and a survey of computer aided methods for mass spectrometry has been devoted to pattern recognition (P26).

The linear learning machine has been applied to extract information on chemical structure of mono functional compounds from retention data in GLC (P12). A 10-dimensional data vector is developed from the use of 10 stationary liquids allowing accurate classification. Linear learning machine and composite segment method were also compared in a study of GC/FTIR data for constructing functional group-specific chromatograms (P11). Interferograms were used directly, so that Fourier transformation was unnecessary which enabled faster computation. However it should be remembered that although linear learning machine is a simple method its use has been critisized in several papers covered in the last review.

The SIMCA method has become popular in structure-activity relationship studies as well as in analytical chemistry. It has seen some very interesting applications to the classification of gas chromotographic profiles of human brain tissues (P34) and cancer cells (P14). These studies also show the advantage SIMCA has when the number of variables exceeds the number of objects. Another application of SIMCA involves the analysis of ionization constants (P9).

The significance of the result for acidity function theory is discussed.

Classification and discrimination methods are becoming accepted tools in food science (P25) and the tobacco industry (P30). Cluster analysis gained an increasingly important role in the past two years and interesting applications in the various fields have appeared in the literature. For example, in order to speed up the library search of spectra, a presearch can be made with a subfile where prototypes represent the whole library. Cluster analysis has been used to identify suitable prototypes for a mass spectral library (P7).

For large data sets as in spectral libraries the standard clustering methods have the disadvantages of demanding considerable computer time and space. To overcome these characteristics, a new scheme was proposed for updating and retrieval from large data bases organized as binary trees (P36).

Cluster analysis has been applied to such diverse studies as accoustic emissions from polymers under stress (P1) and the evaluation of an existing classification of iron meteorites (P28).

One of the operations research models recently studied, a facility location model, has been investigated for clustering purposes (P27). It also contains an algorithm which indicates the significance of a cluster without imposing a priori conditions.

Even patterns of analytical methods for clinical laboratories were examined by clustering techinques (P13). The features characterizing the methods were accuracy, precision, tendency to give erroneous results and tendency to give

systematically different results. Supervised learning methods were then used to determine the significance of these features that lead to cluster formation. The results of the study showed that an objective assessment of the quality of routine analytical methods is feasible.

Preprocessing is the most delicate point of pattern recognition. Useful measurements must first be selected and then the information within the features must be transformed to insure efficient feature utilization. The performance of orthogonal transformations (Fourier, Walsh, Haar) has been the subject of one investigation (P8). The theoretical considerations and conclusions were compared with standard variance and Fischer weights (P3). Feature weighting and feature selection were combined into a single algorithm. The method was evaluated on several different chemical data sets.

The program package ALLOC, applying potential functions for classification, also has a feature selection procedure which is closely related to the ALLOC classification method (P6). It has been compared with the SELECT procedure in ARTHUR and with a statistical procedure of SPSS. In pyrolysis gas chromatography, the normalization of peak areas has been shown to have remarkable effects on feature selection by calculating variance weights (P16). Important features were selected from measurements on coal tar pitches and useful procedures were developed to correct chromatograms from degraded columns.

Feature weighting based on KNN classification has been applied to voltammetric data (P31). Accurate classifications between complicated and

uncomplicated electrode processes were possible. Features based on the Fourier transform gave an excellent classification and could even distinguish mechanisms of the electrode process.

Pattern recognition can be combined with other techniques to obtain improved results. For example, the catalytic activity of transition metals in the hydrolysis of ethane was examined by applying simplex search for a mathematical representation of chemical class structure combined with pattern recognition (P32).

Pattern recognition applications analyzing data from analytical laboratories now appear quite often in several fields. Photolytic degradation of tetrachlorodibenzo-p-dioxin isomers was studied using pattern recognition in an attempt to correlate specific rate data with chlorine substituent locations (P29). Pattern recognition was applied to modelling the Fisher-Tropsch catalytic synthesis (P19), for assessing the impact of a mining operation on a stream in a water quality analysis (P2), and for the examination of oil contamination in the marine environment (P24). A series of publications were made on wine quality studies. Wine samples were classified on the basis of their elemental data (P21), geographic data (P22), sensory scores (P23) and correlations between objective chemical measurements and subjective sensory evaluations were discovered (P20).

Pattern recognition as well as the other areas of multivariate data analysis have truly extended the problemsolving ability of chemists by allowing useful

knowledge to be gained from large amounts of information. These tools which are

heavily used in the chemical industry will be more commonly used in the future.

CONTROL AND OPTIMIZATION

In earlier sections of this review, recent papers on the selection of mathematical models that best represent chemical systems and methods for estimating the parameters of these models were reviewed. The goals of modelling studies are understanding and control. In the latter case, if a selected model is sufficiently predictive, then it can be used to provide accurate estimates of the state of the system once parameters are set and input variable are selected. From this step, it follows that a model representing a system can also be used to find the set of input variables that optimizes, in some sense, the output variables of the model and hence the system. In this section, we examine some selections from the recent literature of analytical chemistry where analytical methods or instruments have been subjected to mathematical optimization. The result is usually an analytical system capable of providing the optimum in resolution, sensitivity or whatever dependent output variable has be n selected as the so-called set point variable.

A fine example of the above has come from the laboratory of George Guiochon (OP4) in France. Using the theory governing reversed-phase liquid chromotography, formulations that relate either analysis time for a given resolution (peak to peak) or the optimal resolution within a given analysis time to experimentally controllable factors are derived. Then by setting the

derivatives of these functions to zero, optimal conditions can be established

for either of the optimization goals. An additional result of this work shows

that, in many cases, isocratic elution is more time consuming than gradient

elution.

In another study involving gradient elution chromatography (OP10),

calculation of the optimal initial concentration and slope of the gradient for

mixtures of compounds with a known relationship between capacity ratio and

composition of the mobil phase has been accomplished.

The use of accurate theoretical relationships to optimize analytical

methods is perhaps the most powerful approach to this problem. Other areas of

analytical chemistry have also taken advantage of this approach. In cyclic

neutron activation analysis, the optimal timing parameters that yield the

lowest limits of detection for shortlived radio nuclides can be determined

using a function that relates detection limits to activities associated with

varying sample matrices and the timing parameters associated with analysis

(OP18). Similarily, the theoretical relationship between reactant

concentrations on one hand and analysis sensitivity and precision on the other

for competitive immunoassays can provide optimal sensitivity and precision

over a wide range of analyte concentrations (OP7).

A good example of improving the efficiency of a measurement procedure is

the application of constant signal-to-noise strategy developed by Enke and

coworkers (OP5). They show how pulse counting experiments can be significantly

improved by varying integration times to match a set statistic.

When an accurate theory relating the controllable factors in an analytical method to the output variable selected for optimization is not available, the optimization problem becomes considerably more complex. In these cases, a nonparmetric optimization algorithm is sometimes used to find the conditions that will yield optimal analyses. In understanding which factors play a role in optimization, the reader should return to the section of this review concerned with experimental design. Since the nonparametric methods discussed next do not use a model of the system it is even more important to include and understand all of the controlling experimental factors and to proceed with an optimization plan with some guidance in order to get the best shot at the true, or global, set of optimum conditions and avoid both a waste of experimental effort and arrival at a false, or local, optimum.

The most popular method for finding the best set of experimental conditions leading to an analytical method or individual analysis optimized for precision, sensitivity, etc. is the sequential simplex method described in many papers reviewed earlier (last review). Since the last review, some improvements to one or more variation in the simplex procedure have been made (OP1, OP20, OP14).

Examples of using one or more of the variations on simplex optimization are becoming more common in the chemical literature as word of its power spreads. The simplex method has been used in reversed-phase liquid

chromatography (OP6), inductively coupled plasma atomic emission spectrocopy (OP3), the synergic extraction of a copper complex (OP13) and for phase correction in FT-NMR spectroscopy (OP16). In addition, work has also appeared that should aid the task of using simplex optimization in optimizing chromatographic resolution (OP17, OP19).

The simplex method is quite efficient in locating an optimal desired response even though it may only be a local optimum. It is most effective when individual experiments are either costly or time consuming. However, when this is not the case, it is often more effective to apply a factorial experimental design, as reviewed in an earlier section, and response surface methodology to optimize an analytical method. Two fine examples of this approach are the optimzation of the separation of four drugs by reversed-phase ion-pair chromatography (OP12) and the enzymatic analysis of ethanol (OP2). Factorial design ensures that the proper number of experiments have been performed so as to accurately estimate the effect of each controllable variable. Then the data are modelled by a polynomial function followed by contour plotting to obtain an accurate pictorial relationship (reponse surface) between the controllable variables and the variable to be optimized. This method is generally more expensive and time consumming than simplex optimzation but has the advantage of showing the chemist the locations of global and local options.

Another method for finding an optimal set of experimental conditions has been used recently in chromatography (OP11, OP15). The method involves the use

of specialized plots called window diagrams and has been proposed for application in electrochemistry and spectroscopy (OP15).

Vollenbrock and Vandeginste (OP21) have used still another approach to understand and optimize not simply an analytical method, but the sum total of several methods working in concert; the analytical laboratory. The authors used queueing theory and digital simulation to study the routing of samples through an analytical laboratory and the effect of alternate routing schemes on the total average delay between the time a sample is submitted and the final results are returned. Their gains were rather dramatic attesting to the benefits that can be obtained when the probelm solving oriented analytical chemist is unchained from a particular analytical method and assumes a broader problem solving role in an organization.

In the authors' opinion, the most exciting work on the application of the principles of control theory to systems involving on-line chemical analysis comes from Jack Frayer and coworkers at the Lawrence Livermore National Laboratory (OP8, OP9). They use a state-of-the-art closed loop control method based on the Smith predictor to control an experimental enzyme reactor containing a saturating element and a large time delay relative to the time constant of the system. Their pioneering work together with the long list of analytical methods that can be adapted to on-line analysis should make the analytical chemist a key figure in modern industrial production.

ARTIFICIAL INTELLIGENCE

Since the application of artificial computer intelligence in chemistry has
not historically been considered chemometrics the topic was ignored in our
last review. However, the topic is developing rapidly and in parallel with
chemometrics. Also, it is really difficult to find the boundaries separating
chemometrics and application of artificial intelligence as scientists in each
field are mutually interested in the other field and papers are presented at
the same conferences.

Chemometrics is based mainly on statistics and numerical mathematics were
artificial intelligence uses mathematical logic. The latter has been applied
almost exclusively to spectroscopy for the interpretation of different types
of spectral data; determination of the molecular structure of organic
molecules. The following systems use information from these different
spectroscopic sources: CHEMICS (A9,A13) uses IR, C13-NMR and proton NMR; SEAC
(A2) IR, proton NMR and UV spectra, Gribov's system (A7) uses MS, NMR and
microwave spectroscopy and ASSIGNER (A12) interprets C13-NMR and IR together.
Others are based on one type of spectroscopy only. For example, CRISE
(A16,A17) works on vibrational spectra (IR and Raman), PAIRS (A11,A20) on IR
spectra, STIRS (A8) on mass spectra, CONGEN (A5) on mass spectra, GENOA (A3)
on C13-NMR spectra.

There are different levels of automatic structure elucidation. Some

systems only aim to find possible functional groups of a molecule and let the chemist reconstruct the molecular structure (A18, A19, A10, A8). Other programs give complete structural candidates for an unknown molecule (A6, A2,A7, A9).

One way to determine the structure of an unknown compound is to predict its spectrum and compare it to the unknown spectrum. This method was followed based on mass spectra (A5,A8), C13-NMR spectra (A6).

Another way to improve the accuracy of a choosen structure or structures is to use spectrum library files, like STIRS (A8) in mass spectroscopy and CRISE (A16, A17) in IR and Raman spectroscopy. Correlation information between functional groups and wavenumber intervals can be stored in correlation tables (A4, A10, A17, A19) a topic recently investigated using information theory (A14). Quantitative evaluation of the usefulness of any change within a given table shows when it is worthwhile to create subfragments (A15).

Elemental composition can be calculated from high resolution mass spectral data (A3) using new methods that minimize the number of steps needed to generate each new candidate and has been relationship between molecular structure and retention indicies based on retention index increments has been investigated (A1),

In order to build an automatic system for spectral interpretation and structure elucidation, a highly computerized laboratory is needed. Some desirable hardware and software features have been discussed (A16).

Computer programs that play accomplished chess are plentiful. However, computer programs that can automatically elucidate the structure of a molecule from spectral data when a molecule's spectra are not explicity members of libraries are still in their infancy. This disparity seems analogous to the differences in salary between football coaches and professors.

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